# Incident ischaemic stroke and Type 2 diabetes

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*Published in:*
Diabetic Medicine

*DOI:*
10.1111/dme.13528

*Publication date:*
2018

*Document Version*
Peer reviewed version

**TITLE:** Incident ischaemic stroke and type 2 diabetes: trends in incidence and case-fatality in Scotland 2004-2013

**Cover Title:** Ischaemic stroke and type 2 diabetes in Scotland

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**Word count:** 2972

**Funding:** Funding for this project came from a Chief Scientist Office post-doctoral fellowship. Funding for diabetes register linkage was provided by the Scottish Government. **DM is funded via an Intermediate Clinical Fellowship from the Wellcome Trust (201492-Z-16-Z)**

**Disclosure Statement:** DM has received consultancy payments from Roche pharmaceuticals and Galecto and is a collaborator in a GSK-funded clinical trial. HC reports grants, personal fees and non-financial support from University of Edinburgh during the conduct of the study; grants and personal fees from Eli Lilly, grants from Astra-Zeneca, Boehringer Ingelheim, Pfizer and Novartis, outside the submitted work; and Stock ownership Roche and Bayer. RSL has served on advisory boards for Novo Nordisk and Eli Lilly and has received travel grants from Novo Nordisk. RJMcC has served on advisory boards for NovoNordisk, Eli Lilly and Sanofi Aventis. NS has served on advisory boards for Amgen, Sanofi, Boehringer Ingelheim, Novo Nordisk, Eli Lilly, Janssen and received grant support from AstraZeneca. SHW received an honorarium from Global MedEd/Astra Zeneca. SHR, BF, CF, JJK, GPL, SMcG and SP have no disclosures.

**Novelty statement**:

- Using population-wide registers we have described contemporary trends in ischaemic stroke incidence and case-fatality in people with and without **a diagnosis of** type 2 diabetes.
- Declines in ischaemic stroke incidence and case-fatality have occurred at the same rate in people with and without **a diagnosis of** type 2 diabetes, **despite attempts to intensify cardiovascular disease risk factor control in people with diabetes**.
- Between 2004 and 2013, the prevalence of **diagnosis of** type 2 diabetes in ischaemic stroke patients in Scotland increased from 13.5% to 20.3%.

**Abstract:**

*Background:* Whether recent trends in ischaemic stroke incidence and case-fatality are similar among people with and without type 2 diabetes is unknown. We describe trends in first ischaemic stroke incidence and case-fatality in adults with and without **a diagnosis of type 2 diabetes prior to their ischaemic stroke event** in Scotland between 2004 and 2013.

*Methods*: Using population-wide hospital admission, death and diabetes datasets, we conducted a retrospective cohort study. Negative binomial and logistic regression models were used to calculate year-specific incidence rates and case-fatality for people with type 2 diabetes and for people without diabetes.

*Results*: During 41.0 million person-years of follow-up there were 69,757 ischaemic stroke events. Type 2 diabetes prevalence among ischaemic stroke patients increased from 13.5% to 20.3% between 2004 and 2013. Stroke incidence rates declined by 2.7% (95% CI: 2.4, 3.0) annually for people with and without diabetes (diabetes/year interaction: Rate ratio (RR) 0.99, (0.98, 1.01)). Type 2 diabetes was associated with an increased risk of ischaemic stroke in men (RR: 1.23 (1.17, 1.30)) and women (1.41 (1.35, 1.48)). Case-fatality was 14.2% and 12.7% in people with type 2 diabetes and without diabetes, respectively. Case-fatality declined by 3.5% (2.7, 4.5) annually (diabetes/year interaction: odds ratio: 1.01 (0.98, 1.02)).

*Conclusion*s: Ischaemic stroke incidence declined no faster in people with **a diagnosis** of type 2 diabetes than in people without diabetes. Increasing prevalence of type 2 diabetes among stroke patients may mean that declines in case-fatality over time will be less marked in the future.

**Introduction:**

Ageing populations, increasing obesity prevalence and improved survival have contributed to increasing type 2 diabetes prevalence in developed countries.[1] Type 2 diabetes is an important cause of cardiovascular disease; ischaemic stroke, for example, is more than one and a half times more common in people with diabetes than in similar populations without diabetes.[2]

It is not known, however, whether recent improvements in the management and treatment of cardiovascular risk factors has reduced this excess risk of stroke in people with diabetes.[3, 4] The overall incidence of ischaemic stroke is estimated to have declined by 13% in high income countries between 1980 and 2010[5]; but it is unclear whether people with type 2 diabetes have experienced similar benefits.

Scotland maintains a national register of all patients with type 2 diabetes, and this register is linked to population-based hospitalisation and mortality registers. Using these large, robust population-wide databases, we have compared trends in ischaemic stroke incidence and case-fatality in men and women with **a diagnosis of** type 2 diabetes and in the population of people without diabetes in Scotland between 2004 and 2013.

**Methods:**

*Data Sources:*

Mid-year population estimates by age, sex and deciles of socio-economic status were obtained from National Records of Scotland. Socio-economic status was defined using the 2012 version of the Scottish Index of Multiple Deprivation, an area-based measure of deprivation which utilises information from seven domains, including income, employment, crime and education to assign deprivation scores to 6,505 small area-zones in Scotland (see http://www.gov.scot/Topics/Statistics/SIMD for further information).

Ischaemic stroke was defined as any hospital admission or death in which the primary diagnosis or cause of death was assigned a tenth revision of International Classification of Diseases (ICD10) code of I63 and I64. Admission and death data were obtained from the National Records of Scotland death registrations and the national hospitalisation register (Scottish Morbidity Record, SMR01), respectively. The SMR01 is a population-based register of hospital admission episodes occurring in Scotland and holds information on patient conditions leading to admission. Unspecified strokes (ICD10 I64) were included in the main analyses since the majority of these events are likely to be ischaemic stroke events, but sensitivity analyses were conducted in which unspecified strokes were excluded. A look-back period of 10 years was used to exclude previous stroke events, identified using the previously defined ICD10 codes and the following ICD9 codes; 433, 434 and 436. **This lookback period is consistent with the definition of incident ischaemic stroke events in data published by Information Services Division, Scotland. It ensures a consistent lookback period for all individuals which is important because electronic records only go back to 1981 and lifetime data are not available**. Case fatality was defined as a death within 30 days following a hospital admission with ischaemic stroke.

Type 2 diabetes status was ascertained by linkage to a research extract of the Scottish Care Information – Diabetes dataset. This national register collates demographic and clinical data from primary and secondary care clinics in Scotland. Since 2004, this register covers over 99.5% of people with a diagnosis of diabetes in Scotland. For research purposes, an algorithm which utilises clinician recorded diagnosis, prescription data and age at diabetes diagnosis was used to ascertain diabetes type. **Presence of type 2 diabetes was defined for this study on the basis of a diagnosis of type 2 diabetes prior to hospital admission or death due to ischaemic stroke.**

Approval for generation and analysis of the linked dataset was obtained from the Caldicott guardians of all Health Boards in Scotland, the Privacy Advisory Committee of the Information Services Division of NHS National Services Scotland (ISD) and the national multi-centre research ethics committee.

*Statistical Analyses*

Analyses were conducted in people without a previous history of stroke, aged between 18 and 89 years and who had available data on socio-economic status. The study group consisted of individuals with a diagnosis of type 2 diabetes and a comparison group of individuals without a record of any type of diabetes **prior to the ischaemic stroke event. To calculate the event numbers and person-time for people without diabetes, the number of incident stroke events and person time at risk for the population of people with any type of diabetes were subtracted from the total number of events and person-time for the whole population (see Supplementary Figure 1)**. The start and end dates were January 1st 2004 and December 31st 2013 respectively. Individual person-time was estimated as the number of days between study start-date (or date of diabetes diagnosis if diagnosis occurred during the study period) until date of incident event, death or study end-date.

Negative binomial regression models were used to estimate incidence rates and rate ratios by age, sex, calendar year, diabetes status and deprivation. Age in years was divided by ten so that each increment was a decade. Deprivation decile 1 represented the most deprived group and deprivation decile 10 represented the least deprived group. Calendar year was included in models as a linear term. To investigate whether differential changes in ischaemic stroke risk have occurred in people with type 2 diabetes and the comparison group, the final model included a two-way interaction term for calendar year and diabetes status. A three-way interaction term between sex, calendar year and diabetes status was also included to

investigate whether the risk of ischaemic stroke is greater in women than in men with type 2 diabetes and whether this relationship has changed over time. All other interaction terms between age, sex, deprivation, calendar year and deprivation were included if the exponentiated coefficient was $\geq 1.05$ or $\leq 0.95$.

Logistic regression models were used to model case-fatality by year, sex and diabetes status. For illustration, incidence and case-fatality rates are presented for men and women aged 70 years in deprivation decile 5.

Statistical analyses were conducted in R, version 3.2.2

**Results:**

Overall, 69,757 ischaemic/unspecified stroke events occurred during 41.0 million person-years of follow-up. Of these events 36,276 were coded specifically as ischaemic stroke. Among people with **a pre-existing diagnosis of** type 2 diabetes there were a total of 11,437 ischaemic/unspecified stroke events during 1.9 million person-years. Table 1 describes the total number of ischaemic/unspecified stroke events by year, sex and diabetes status. Briefly, among ischaemic stroke patients, the proportion of people with type 2 diabetes increased from 13.5% in 2004 to 20.3% in 2013. Overall, the proportion of people dying within 30 days of hospital admission declined from 13.8% to 10.7%. Crude case fatality was higher among people with type 2 diabetes compared to people without diabetes (14.2% vs. 12.7%) and in women compared to men (14.9% vs 10.9%).

In models adjusted for age, sex and deprivation and diabetes, ischaemic/unspecified stroke incidence rates (95% CI) declined by 2.7% (2.4, 3.0) each year overall. Rates of decline were similar in people with type 2 diabetes to those without diabetes (Rate ratio (RR) per year for interaction between diabetes and year: 0.99 (0.98, 1.01), p-value=0.91). Incidence rates were higher for men than women and in people with type 2 diabetes than in people without

diabetes (Figure 1). Overall, RRs for the association between type 2 diabetes and ischaemic/unspecified stroke risk for the whole study period were 1.41 (1.35, 1.48) for women and 1.23 (1.17, 1.30) for men. The RRs for the association between type 2 diabetes and ischaemic stroke were 1.43 (1.33, 1.53) and 1.42 (1.33, 1.52) in women in 2004 and 2013, respectively. In men, the RRs were 1.28 (1.20, 1.37) in 2004 and 1.21 (1.13, 1.30) in 2013. Type 2 diabetes was associated with higher rate ratios in women than men (RR for diabetes/sex interaction: 1.15 (1.09, 1.27) p-value <0.001) and this effect did not change during the study period (RR for diabetes/sex/year interaction: 1.01 (0.99, 1.02), p-value: 0.472). Following stratification by age, sex-differences in risk of incident ischaemic stroke were most apparent in people aged below 60 years (**Supplementary Figure II**).

When ischaemic stroke deaths prior to hospital admission were excluded, type 2 diabetes was associated with an increased risk of ischaemic stroke in men (RR: 1.26 (1.20, 1.33)) and women (1.45 (1.37, 1.52)).

Case-fatality at 30 days declined in relative terms by 3.6% per year (95% CI: 2.7, 4.5) in the study population and there was no significant difference in rates of decline by type 2 diabetes status (diabetes/year interaction: odds ratio 1.01, **(0.98, 1.02)**, p-value= 0.58) (Figure 2). Case fatality was higher for people with type 2 diabetes than in people without diabetes (age and deprivation adjusted odds ratio: 1.18 (1.09, 1.29) for women and 1.15 (1.05, 1.26) for men).

*Sensitivity Analyses*

When unspecified stroke events (ICD-10 code: I64) were excluded (n=33,481, 48.0%) from the analyses, the findings were similar to the primary analyses (**Supplementary Table I, Supplementary Figures III & IV**). Incidence rates of ischaemic stroke declined by 1.26% (0.66, 1.87) per year in people with type 2 diabetes and in people without diabetes (diabetes/year interaction: RR 0.99 (0.98, 1.01) p-value= 0.91). Overall, type 2 diabetes

conferred a 40.5% (31.2, 50.2) and 19.2% (11.7, 27.3) excess risk of ischaemic stroke among women and men with type 2 diabetes compared to people without diabetes.

**Discussion:**

*Main findings:*

Despite major initiatives to improve cardiovascular risk factors in people with type 2 diabetes, ischaemic stroke incidence rates between 2004 and 2013 in people with **a diagnosis of** type 2 diabetes in Scotland fell no faster than those in the general population.[6, 7] This trend and the growing prevalence of type 2 diabetes means that one-fifth of people who have an ischaemic stroke now have type 2 diabetes, a trend which is likely to have important implications for reductions in ischaemic stroke case-fatality in coming years.

*Relation to other studies:*

As has been shown elsewhere, incidence rates of stroke in people with and without diabetes continued to decline between 2004 and 2013, reflecting improved treatment of hypertension and dyslipidaemia as well as population-wide improvements in dietary salt intake and smoking prevalence.[8, 9] Despite these improvements, type 2 diabetes continues to confer an excess risk of ischaemic stroke and this study indicates that the excess risk has remained unchanged.

In our study, type 2 diabetes was associated with a 45% and 26% increased risk of hospital admission for ischaemic stroke in women and men. This represents a considerably smaller excess risk than observed in previous studies.[2, 10] For example, one study based on English data, type 2 diabetes was associated with a three and a half fold increased risk of hospital admission for stroke between 2004 and 2009.[10] **The discrepancy in strength of association may be partly explained by the exclusion of stroke deaths which occurred prior to hospital admission from the analyses presented in the English study. These deaths**

**accounted for 11.7% and 13.8% of stroke events in people with and without a diagnosis of diabetes respectively in our data.** Few other studies have presented contemporary trends in the association between type 2 diabetes and ischaemic stroke and comparisons are difficult due to differences in definitions of stroke and diabetes. For example, in the US, the relative risk of stroke associated with diabetes declined from 2.5 (2.2, 2.7) in 2000 to 1.5 (1.1, 2.0) in 2010, but this study did not distinguish between type 1 and type 2 diabetes nor were estimates provided for stroke subtypes.[3]

In an effort to improve health outcomes of people with chronic diseases such as type 2 diabetes, the UK implemented the Quality and Outcomes Framework in 2004. This initiative incentivised general practices to reach a series of targets in the clinical management of chronic diseases and was expected to improve health outcomes for people with diabetes relative to the general population. Between 2004 and 2013, smoking prevalence declined and the management of hypertension, cholesterol and hyperglycaemia improved in people with type 2 diabetes.[11] In addition it appears that diabetes may be being diagnosed earlier over time based on declining prevalence of retinopathy soon after diagnosis, perhaps as a result of wider **diabetes** screening.[12] While comparable data for secular trends in cardiovascular disease risk factors in the Scottish population as a whole are limited, it is apparent that rates of obesity and hypertension have remained higher among people with type 2 diabetes compared to the general population.[13] For example, 63% of the Scottish adult population were overweight or obese in 2014, compared to 87% of adults with type 2 diabetes in 2014.[11, 14] Therefore despite some improvements, people with type 2 diabetes continue to have worse cardiovascular disease risk factor profiles than people without diabetes and subsequently remain at considerably greater risk of ischaemic stroke.

In agreement with previous findings, type 2 diabetes had a greater relative influence on ischaemic stroke relative risk in women than men and this sex difference did not change

considerably over time in our study. A recent large meta-analysis reported a 27% higher relative risk of stroke for the effect of diabetes in women compared to men.[15] However, this RR ratio became only borderline significant upon the exclusion of haemorrhagic stroke (RR ratio: 1.25 [1.01-1.54]) and when studies in which baseline data were collected before 1985 were excluded (RR ratio: 1.21 [1.01, 1.46]). Similar non-significant sex differences in risk of stroke were also observed in the Clinical Practice Research Datalink database and the General Practice Research Database in the UK. [2, 16] In both studies the sex difference was more apparent among people aged below 60 years, a finding that we have replicated here (**Supplementary Figure II).**

Several explanations for the sex difference in diabetes-related excess risk of stroke have been proposed.[17] Firstly, while women in the general population usually have more favourable cardiovascular disease risk profiles than men, women exhibit greater deteriorations in cardiovascular disease risk profiles with the development of diabetes than men. For example, two UK-based studies have demonstrated that men typically have lower body mass index at diagnosis of type 2 diabetes than women, suggesting that women need to gain more weight to develop diabetes than men, and this is particularly marked at younger ages of diagnosis.[18, 19] Furthermore, several studies have shown that the relative difference in levels of cardiovascular disease risk factors including levels of insulin resistance, lipids, fibrinogen and diastolic blood pressure between people with and without diabetes are greater in women than men.[20-22]

Secondly, differences in diabetes management may also contribute to this sex difference with some evidence to suggest that women with type 2 diabetes are less likely to be prescribed statins, anti-hypertensive agents and beta-blockers compared to men.[17, 23] Similarly, in a cross-sectional study consisting of 10,191 people with type 2 diabetes in Tayside, Scotland, women were less likely to have their cholesterol or blood pressure recorded than men.[24]

Thirdly, poor glucose control may have a more adverse effect on women than men in terms of stroke risk.[25] Finally, even when treated similarly, women with type 2 diabetes have been shown to be less likely to achieve cardiovascular disease risk factor targets than men.[24, 26-28] In Scotland, women with diabetes were less likely to achieve all four targets for glycated haemoglobin, cholesterol, blood pressure and smoking cessation than men (OR: 0.75 [0.67, 0.84]).[24] Accordingly, women with type 2 diabetes appear to have a greater cardiovascular risk factor burden compared to their counterparts without diabetes, emphasising a greater requirement for more aggressive risk factor monitoring and treatment in women with diabetes.

Despite this sex difference in relative risks, fatal and non-fatal stroke events are more common in men than women after adjusting for age and deprivation, regardless of diabetes status. Improvements in primary and secondary prevention in both men and women prior to and following diabetes diagnosis should therefore remain a priority.

Our findings of proportionately more patients with stroke having diabetes (now one in five at stroke presentation) are relevant to primary and secondary prevention of stroke. Of note, recent RCTs show that some of the newer diabetes therapies (e.g. GLP-1 receptor agonists – semaglutide, not yet licenced) may be associated with reduced stroke risk in people with diabetes[29] while pioglitazone may have survival benefits post stroke in patients with insulin resistance[30]. Further research is therefore required to determine to what extent more recent diabetes therapies can lower the risk of stroke or improve survival post stroke.

*Strengths/Weaknesses:*

This study utilised population-based data to provide contemporary, long-term estimates which are representative of the entire Scottish population. Diabetes status was ascertained

using the national diabetes register rather than through hospital admission databases which have been shown to under-report diabetes cases.[31]

Unlike many previous studies which have been unable to distinguish between type 1 and type 2 diabetes, we have been able to provide estimates for ischaemic stroke risk specifically for people with type 2 diabetes. Significant differences in the aetiology, diagnosis and treatment of type 1 and type 2 diabetes are likely to contribute to considerable differences in stroke risk which would have been masked by combining these conditions. Furthermore, diabetes status is validated in the diabetes register using an algorithm which utilises prescription and age at diagnosis data.[32] The risk of misclassifying type 1 diabetes cases as type 2 diabetes is therefore minimised.

There are some limitations of this study which should be acknowledged. There are likely to be inaccuracies in the coding of the event of interest since these are routinely recorded data. For example, a recent study identified that 25% of stroke events identified in the Scottish Stroke Care Audit were not recorded in the SMR01 dataset in 2010.[33] Unidentified strokes in the SMR01 dataset are likely to have occurred due to errors in the coding of primary diagnoses by coders and therefore while this represents a significant proportion of stroke events it seems unlikely that the recording of these events differed systematically by diabetes status.

The lack of availability of clinical data for the population of people without diabetes prevented any further analyses of differences in cardiovascular disease risk factors by diabetes status to explain the observed trends. **Furthermore, the duration of diabetes is likely to be a relevant risk factor for stroke in people with diabetes but this was not explored in these analyses**.

**Finally, some people with diabetes that is first diagnosed during their stroke admission will have been included in the population without diabetes. This misclassification may have led to the underestimation of the strength of the association between type 2 diabetes and ischaemic stroke, though it is uncertain whether this would also have affected whether the association between type 2 diabetes and ischaemic stroke varied over time.**

*Conclusions:*

During the 10-year period between 2004 and 2013, stroke incidence declined regardless of diabetes status but risk of stroke remained 29-39% higher among people with a **diagnosis of** type 2 diabetes than in the population of people without diabetes, despite significant efforts to improve cardiovascular disease risk factor management in people with type 2 diabetes. The relative effect of type 2 diabetes on stroke risk was higher in women but absolute risk was higher in men indicating that primary and secondary prevention of both diabetes and ischaemic stroke are important in both sexes. Given the rising prevalence of diabetes in stroke patients, further research investigating the effect of modern diabetes therapies on stroke incidence and case-fatality are warranted.

**Acknowledgements:**

Aspects of the work presented in this manuscript have been presented at the Diabetes UK Professional Conference 2017 and at the European Diabetes Epidemiology Group annual meeting 2017.

**Contributors:** The study was conceived by SHW, DAMcA and SHR; data preparation was carried out by JJK and SHR conducted the statistical analyses. SHR wrote the first draft of the paper. All authors contributed to the interpretation of the findings and the paper's critical

revision. All authors have approved the final version of the manuscript. SHR is responsible for the integrity of the work.

**Figure Legends:**

**Figure 1:** Incidence rates of ischaemic stroke (ICD10: I63, I64) per 1,000 person-years for (A) women and (B) men with type 2 diabetes and without diabetes between 2004 and 2013. The lines represent predicted incidence rates for men and women aged **70** years and in deprivation decile 5. Model adjusted for the following interactions: sex/diabetes, sex/deprivation, deprivation/**diabetes** (p-values all <0.001).

**Figure 2**: Case fatality (%) following incident stroke for (A) women and (B) men with type 2 diabetes and without diabetes between 2004 and 2013. The lines represent predicted case-fatality for men and women aged 70 years and in deprivation decile 5.

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**Table 1.** Total number of stroke events (I63, I64), case-fatality and person time at risk for people aged 18-89 years, by diabetes status, sex and year in Scotland between 2004 and 2013.

| | Female | | | | | | Male | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Population without diabetes | | | Type 2 diabetes | | | Population without diabetes | | | Type 2 diabetes | | |
| Year | Total events | Case-fatality (% of hospital admissions) | PYs (1000) | Total events | Case-fatality (% of hospital admissions) | PYs | Total events | Case-fatality (% of hospital admissions) | PYs (1000) | Total events | Case-fatality (% of hospital admissions) | PYs (1000) |
| 2004 | 3550 | 468 (16.0) | 2016 | 505 | 73 (16.4) | 65 | 3026 | 312 (11.8) | 1804 | 525 | 45 (9.6) | 76 |
| 2005 | 3358 | 420 (14.8) | 2026 | 516 | 79 (17.4) | 70 | 2903 | 326 (12.6) | 1815 | 564 | 74 (14.9) | 82 |
| 2006 | 3130 | 411 (15.5) | 2034 | 507 | 75 (16.5) | 75 | 2936 | 314 (12.1) | 1827 | 509 | 59 (12.9) | 88 |
| 2007 | 2994 | 401 (15.8) | 2046 | 485 | 75 (17.6) | 79 | 2696 | 274 (11.4) | 1842 | 535 | 68 (14.1) | 94 |
| 2008 | 3114 | 439 (16.5) | 2056 | 499 | 83 (20.2) | 82 | 2850 | 298 (11.7) | 1855 | 586 | 78 (14.9) | 99 |
| 2009 | 3049 | 380 (14.4) | 2064 | 567 | 90 (18.3) | 87 | 2755 | 254 (10.1) | 1865 | 622 | 60 (10.3) | 105 |
| 2010 | 2975 | 364 (13.9) | 2075 | 577 | 77 (15.2) | 90 | 2701 | 258 (10.5) | 1877 | 610 | 64 (11.5) | 111 |
| 2011 | 2856 | 338 (13.3) | 2088 | 533 | 71 (15.3) | 94 | 2673 | 210 (8.6) | 1894 | 639 | 81 (13.8) | 116 |
| 2012 | 2737 | 312 (13.0) | 2092 | 620 | 85 (15.5) | 97 | 2650 | 214 (8.7) | 1896 | 668 | 73 (11.6) | 121 |
| 2013 | 2737 | 310 (13.0) | 2094 | 635 | 75 (13.4) | 100 | 2630 | 198 (8.2) | 1901 | 735 | 68 (10.0) | 127 |
| Total | 30500 | 3843 (14.7) | 20590 | 5444 | 783 (16.5) | 838 | 27820 | 2658 (10.6) | 18577 | 5993 | 670 (12.3) | 1020 |

PYs: Person-years